RESPONSE TO OFFICE ACTION DATED 14 FEBRUARY 2011

1. Rejection Under 35 U.S.C. §103 over 7-Way Combination of Nichols, Corrigan, Pfeiffer, Bronzava, Marquis, Rimpler and Dinan

Claims 10-20, 27, 29-71, and 83 stand rejected under 35 U.S.C. §103(a) as allegedly unpatentable over 7 documents: U.S. Patent No. 4,501,890 (Nichols) in view of Corrigan, *et. al* (2000) Depression and Anxiety, 1:56-65 (Corrigan), Pfeiffer (2002), Drugs Aging, 19(8): 561-570 (Pfeiffer), and in further view of U.S. Patent Publication No. 2005/0038015 (Bronzava), U.S. Patent No. 6,350,773 (Marquis), U.S. Patent No. 2003/0180332 (Rimpler), and U.S. Patent Publication No. 2005/0037983 (Dinan). This 7-way rejection is respectfully traversed.

At the outset, the Examiner cites **seven (7) documents** to support the obviousness rejection. The shear volume of references cited and the evidence of record supporting that there is no reasonable expectation of success that rotigotine could effectively treat depression (as articulated more clearly below) evidence that the Examiner has failed to establish a presumption of *prima facie* obviousness." *See* 2 *Chisum on Patents* § 5.04(1)(e)(vi) ("[t]he requisite prior art suggestion to combine [references] becomes less plausible when the necessary elements can only be found in a large number of references..."); *see also Ling-Temco-Vought, Inc. v. Kollsman Instrument Corp.*, 372 F.2d 263, 268–69 (2d Cir. 1967) ("[i]t is apparent that the more numerous the references and the more remote the cited art from the subject matter of the patent in suit, the less likely it becomes that a person having ordinary skill in the art would have arrived at the result reached by the patent in suit"); *Eli Lilly & Co. v. Teva Pharmaceuticals*, 2004 WL 1724632, at *23 (S.D. Ind. July 29, 2004), *aff'd*, 2005 WL 1635262 (Fed. Cir. July 13, 2005) (citing *Chisum*).

1.1. Claims 10-20, 27, and 29-71

A. There Is No Reasonable Expectation Of Success That Rotigotine Could Effectively Treat Depression.

The Office Action (p. 12) states "there is an obviousness to try and expectation of success for rotigotine to have anti-depressive activity because the compound of Nichols and rotigotine are both D_2 agonists and treat Parkinson's disease." However, the evidence of record establishes the exact opposite conclusion, *i.e.* knowledge that rotigotine is a D_2 agonist, without the complete receptor profile, and knowledge that rotigotine is effective to treat Parkinson's disease would not provide a reasonable expectation of success for at least the following reasons.

i. The Entire Receptor Profile Is Needed to Determine Effectiveness In Treating Depression.

Effectiveness of a compound is not limited to its D_2 receptor profile. Effectiveness is based, in part, by the compound's complete receptor profile. As set forth in Scheller, *et al.* (2009) Naunyn-Schmiedeberg's Arch Pharmacol 379:73-86, at 73, "[t]o fully understand the pharmacological actions of rotigotine" or any compound, one must understand "its extended receptor profile." For example, Wang, *et. al* (2007) Chinese J. of Physiology 502(2): 63-68 (herein "Wang") reports on the effects of apomorphine (APO), an agonist for the D_1 and D_2 receptors. Rather than just concluding that since APO is a D_2 agonist it would be effective, Wang studies the effect. Accordingly, the evidence of record clearly establishes that merely knowing rotigotine is a D_2 agonist without the full receptor profile, does not establish a reasonable expectation of success that rotigotine would be successful – *i.e.*, the Office Action's rationale for reasonable expectation of success is contrary to the art of record.

Furthermore, in the RCE and Response dated 18 November 2010, Applicant submitted Bertaina-Anglade. Bertaina-Anglade discusses the effectiveness of dopamine agonists in the treatment of depression and reports clinical trials for the D_2-D_3 receptor agonist, pramipexole. However, Bertaina-Anglade still questions the efficacy of ropinerole, another D_2-D_3 receptor agonist, to treat depression. *See* Bertaina-Anglade, *et. al* (2006) European Journal of Pharmacology 548: 106-114 at pg. 107. The Examiner fails to even address such evidence in

the present Office Action. *See* MPEP 707.07(f) ("[w]here the applicant traverses any rejection, the examiner should, if he or she repeats the rejection, take note of the applicant's argument and answer the substance of it").

In other words, the Examiner fails to answer the question: if one of ordinary skill in the art could predict efficacy from D_2 affinity, why would Wang and Bertaina-Anglade be unable to predict the effectiveness of APO and ropinerole from pramipexole? The answer is one of ordinary skill could not predict such effectiveness just by simply knowing that rotigotine was a D_2 agonist. Accordingly, the Office Action fails to provide sufficient evidence to establish that one of ordinary skill in the art, without knowledge of the full receptor profile, could predict effectiveness in treating depression.

ii. Evidence of D_2 Agonist Failure to Treat Depression, Although Used in Treating Parkinson's Disease,.

Wang's conclusions on APO (a D_2 agonist) is strong evidence that one of ordinary skill in the art could not predict effectiveness in treating depression based on rotigotine being a D_2 agonist and useful in treating Parkinson's disease. APO is both a D_2 agonist and used in the treatment of Parkinson's disease, however APO failed to treat depression. *See* http://en.wikipedia.org/wiki/Apomorphine (printed 6 June 2011). Wang concluded that APO's "excessive stimulation of D_1 receptor may participate in the failure of coping behavior leading to learned helplessness and therefore in the pathophysiological mechanisms underlying the development of depression." In response, the Office Action (p. 11) states "[i]n regards to Wang et al., since at the time of the invention, rotigotine was known to be a D2 agonist, particularly a 15:1 ratio selection of D2 over D1 (see Belluzzi et al. abstract), one skilled in the art would not expect an excessive stimulation of the D1 receptor." The opinion that one of ordinary skill in the art would not expect rotigotine to have an "excessive stimulation of the D1 receptor" is made without any citation to authority. In particular, Wang, for example, does not provide a ratio of D_2 over D_1 for APO or a definition for "excessive stimulation." Accordingly, there is no evidence in the cited art that the ordinary artisan would have known whether rotigotine excessively stimulates the D_1 receptor or some other receptor when administered to negatively or positively affect the treatment of depression.

In other words, the evidence of record exemplifies that a D_2 agonist and compound used in treating Parkinson's disease, like APO, can fail to treat depression, thus there is unpredictablity in this art. For this reason alone, the Office Action's statement that "there is an obviousness to try and expectation of success for rotigotine to have anti-depressive activity" because rotigotine is both a D_2 agonist and useful in treating Parkinson's disease is insufficient to support a presumption of *prima facie* obviousness.

iii. Nichols' and Corrigan's Compounds Are (1) Structurally Different and (2) Do Not Share the Same Receptor Profile or D_2 Agonist Activity as Rotigotine.

Further, rotigotine is structurally and chemically different than the compounds reported in Nichols, Corrigan, and Muscat *et al* (1992) Biological Psychiatry, 31:9, 937-946 (not cited in rejection) (hereinafter Muscat). These numerous differences further distance any expectation of rotigotine's depression performance from the compounds in the cited art. Applicant incorporates the argument in the RCE and Response dated 18 November 2010, at p. 13 which depicts the structural differences between Nichols' compounds and rotigotine. Additionally, Corrigan and Muscat report on D_2 agonists that are chemically and structurally different compounds from rotigotine. The Office Action fails to address such structural difference and the role that such structural differences can play in predicting effectiveness in drug therapy. *See* MPEP 707.07(f) ("the examiner should, if he or she repeats the rejection, take note of the applicant's argument and answer the substance of it").

In any event, rotigotine is even further removed from the cited art compounds because:

(1) Nichols states that the "compounds represented by Formulas III and IV are dopamine (D-2) agonists substantially devoid of other agonist or antagonist (blocking) activities." *See* col. 3, lines 20-23 (emphasis added). Contrary to the compounds reported in Nichols, rotigotine is not substantially devoid of other agonist or antagonist activity

(2) Further, rotigotine demonstrates a preference for the D_3 receptor not the D_2 receptor. "In standard binding assays, rotigotine demonstrated the highest affinity for dopamine receptors, particularly the dopamine **D_3** receptor (K_i = 0.71 nM) **with its affinities to other dopamine receptors** being (K_i in nM) $D_{4.2}$ (3.9), $D_{4.7}$ (5.9), D_2 (13.5), $D_{4.4}$ (15), and

D_1 (83)...In newly developed reporter-gene assays for determination of functional activity, rotigotine behaved as a full agonist at dopamine receptors (rank order: D_3>D_{2L}>D_1=D_5>$D_{4.4}$) with potenticies 2,600 and 53 times higher than dopamine at dopamine D_3 and D_{2L} receptors, respectively...Thus, in respect to Parkinson's disease, rotigotine can be characterized as a specific **dopamine receptor agonist with a preference for the D_3 receptor over D_2 and D_1 receptors**." *See* Scheller, *et al.* (2009) Naunyn-Schmiedeberg's Arch Pharmacol 379:73-86, at 73 (emphasis added).

(3) The Office Action cites Corrigan as reporting "pramipexole, a D2 receptor agonist, treating depression safely in individuals with major depression." *See* Office Action, at p. 4. However, pramipexole is a non-ergolinic agonist of the D_2 subfamily of dopamine receptors (D_2, D_3 and D_4), having strongest affinity for D_3. Pramipexole shows only weak or no affinity for D_1; 5-hydroxytryptamine (5-HT) receptors such as 5-HT_{1A} and 5-HT_7; and for alpha-adrenergic receptors such as α2B or α2C. *See* USSN 11/764,907, at paragraph 29. Unlike pramipexole, Applicant's specification as filed at paragraph **[0005]**, teaches "[i]t has now surprisingly been found that rotigotine described as a dopamine agonist…binds both to α2 receptors and to the 5-HT_{1A}" receptors. Thus, rotigotine clearly has a different chemical profile than pramipexole.

Therefore, the Office Action's rationale that there is an expectation of success based on an alleged common action on the D_2 receptor is in error and cannot be used as a basis for establishing a reasonable expectation of success. The cited art reports on structurally different and chemically different compounds from rotigotine, and thus, regardless of the effectiveness of structurally and chemically different compounds, one of ordinary skill in the art could not predict effectiveness in treating depression with rotigotine from the cited compounds.

iv. There Is an Unreasonable Amount of Experimentation With No Guidance From Cited Art.

For the reasons discussed above, there is nothing within the cited documents that provide any guidance to arrive at the claimed invention. Because knowing rotigotine is a D_2 agonist and effective at treating Parkinson's disease does not establish motivation or a reasonable expectation of success in treating depression with rotigotine. As discussed in the

Request for Continued Examination and Response dated 18 November 2010, the ordinary artisan would have to make at least the following unguided steps:

1. pick a compound considered to act on at least one dopamine receptor,
2. then choose one that acted on at least the D_2 receptor but with a preference for D_3 (opposite of what is suggested in Nichols and the Office Action) and without over stimulation of D_1 (as discussed by Wand), and
3. select rotigotine (a dopamine receptor agonist with a preference for the D_3 receptor over D_2 and D_1 receptors).

Accordingly, without any guidance in the art, there is no pattern of preference for choosing rotigotine with a completely different receptor profile from the Nichol's compounds and Corrigan's report on pramipexole. At best, the very large number of possible compounds (128 D_2 acting compounds, with at least 30 being D_2 agonists or partial agonists) provides only an invitation to "try" or "experiment" on the large number of agonists. It is apparent that in the instant case, "what would have been 'obvious to try' would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful." *In re O'Farrell*, 853 F. 2d 894, 903 (Fed. Cir. 1988). "In such circumstances, where a defendant merely throws metaphorical darts at a board filled with combinatorial prior art possibilities, courts should not succumb to hindsight claims of obviousness." *In re Kubin*, 561 F.3d 1351, 1359 (Fed. Cir. 2009), emphasis added.

In conclusion, there is no reasonable expectation of success at least because:

- Rotigotine's full receptor profile was unknown;
- The documents of record teach that without the full receptor profile, the pharmacological effects were unpredictable;
- The documents of record conclusively establish that just because a compound is a D_2 agonist and used to treat Parkinson's disease, does not predict effectiveness in treating depression (*see,* for example, APO);
- Rotigotine does not share the same D_2 activity as the Nichols' compounds, and

in fact demonstrates mixed dopamine receptor activity, favoring the D_3 receptor;

- Rotigotine does not share the exact same receptor profile as pramipexole; and
- The amount of experimentation is too great to provide any predictability or reasonable expectation of success. In order for an invention to be "obvious to try", there has to be a finite number of identified, predictable potential solutions to the recognized need or problem. MPEP §2143, citing *KSR International Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 82 USPQ2d 385 (2007).

Therefore, for at least these reasons, the seven (7) cited documents, alone or in combination, fail to establish a presumption of *prima facie* obviousness.

B. Conclusion: 7-way 35 USC §103(a) Rejection

Notwithstanding the Examiner's comments with regard to specific dependent claims, each of Claims 11-20, 27, and 29-71 is nonobvious over Nichols in view of Pfeiffer and Corrigan, and in further view of Bronzava, Marquis, Rimpler, and Dinan for at least the same reasons that Claim 10 is nonobvious.

1.2 Claim 83

Although Claim 83 is patentably distinct from Claim 10, Claim 83 is nonobvious over Nichols in view of Pfeiffer and Corrigan, and in further view of Bronzava, Marquis, Rimpler, and Dinan for at least the same reasons that Claim 10 is nonobvious.

Furthermore, Claim 83 recites a method for treating endogenous depression in a mammal. The Office Action fails to specifically address independent Claim 83. Moreover, the cited documents fail to provide any expectation of success in treating depression with rotigotine, much less rotigotine treating endogenous depression, a "species" of depression. As such, the Office Action further fails to establish a presumption of *prima facie* obviousness of Claim 83 over the cited art.

Withdrawal of the present 35 U.S.C. §103(a) rejection over the seven-way combination of Nichols, Corrigan, Pfeiffer, Bronzava, Marquis, Rimpler and Dinan is respectfully requested.

2. Rejection Under 35 U.S.C. §103 Over 9-Way Combination of Nichols, Pfeiffer, Corrigan, Bronzava, Marquis, Rimpler, Dinan, Lauterbach and Hoffman

Claims 23-26 stand rejected under 35 U.S.C. §103(a) as allegedly unpatentable over 9 documents: Nichols in view of Corrigan and Pfeiffer, in further view of Bronzava, Marquis, Rimpler, and Dinan, and in further view of WO 02/089777 (Lauterbach) and U.S. Patent No. 4,769,028 (Hoffman). This 9-way rejection is respectfully traversed.

The Examiner cites nine (9) documents to support the obviousness rejection of Claims 23-26. *See* 2 *Chisum on Patents* § 5.04(1)(e)(vi) ("[t]he requisite prior art suggestion to combine [references] becomes less plausible when the necessary elements can only be found in a large number of references…"); *see also Ling-Temco-Vought*, 372 F.2d at 268–69 ("[i]t is apparent that the more numerous the references and the more remote the cited art from the subject matter of the patent in suit, the less likely it becomes that a person having ordinary skill in the art would have arrived at the result reached by the patent in suit"); *Eli Lilly & Co.*, 2004 WL 1724632 at *23 (citing *Chisum*). Additionally, Claims 23-26 ultimately depend from Claim 10. Although not specifically rejected, a presumption of *prima facie* obviousness of Claim 10 (and thus of any claim dependent therefrom) over Nichols, Corrigan, Pfeiffer, Bronzava, Marquis, Rimpler, Dinan, Lauterbach and Hoffman, or any combination of the 9 documents, has not been established. The addition of Hoffman and Lauterbach fails to cure the deficiencies of Nichols, Corrigan, Pfeiffer, Bronzava, Marquis, Rimpler, Dinan, or any combination thereof (*see* Section 1, above). Lauterbach reports on the measured effects of rotigotine only on Parts II and III of the Unified Parkinson's Disease Rating Scale (UPDRS). Depression is only one aspect of behavior and mood included in Part I of the UPDRS. However, Lauterbach does not report that rotigotine has effective anti-depressive properties. Even if, *arguendo,* Hoffman "teach[es] a medical plaster that releases the active agent in a matrix and comprises adhesive properties" (Office Action, p. 7), Hoffman fails to disclose or teach rotigotine or depression. Accordingly, Hoffman does not provide any teaching or expectation regarding rotigotine's effect on the treatment of depression.

Since Lauterbach and Hoffman fail to cure the deficiencies of Nichols, Corrigan, Pfeiffer, Bronzava, Marquis, Rimpler, Dinan, or any combination thereof, the fact remains

that rotigotine was not known to have antidepressant activity prior to the present invention. Therefore, the nine (9) cited documents, alone or in combination, fail to establish a presumption of *prima facie* obviousness of Claim 10.

Notwithstanding the Examiner's comments with regard to Claims 23-26, each of Claims 23-26 depend from Claim 10 and are nonobvious for the same reasons Claim 10 is nonobvious over Nichols, Corrigan, Pfeiffer, Bronzava, Marquis, Rimpler, Dinan, Lauterbach and Hoffman or any combination thereof.

Withdrawal of the present 35 U.S.C. §103(a) rejection is respectfully requested.

3. Rejection Under 35 U.S.C. §103 Over 8-Way Combination of Nichols, Corrigan Pfeiffer, Bronzava, Marquis, Rimpler, Dinan, and den Daas

Claims 21 and 22 stand rejected under 35 U.S.C. §103(a) as allegedly unpatentable over 8 documents: Nichols in view of Corrigan and Pfeiffer, in further in view of Bronzava, Marquis, Rimpler, and Dinan, and in further view of den Daas, et al. (1990) Naunyn-Schmeideberg's Arch Pharmacol, 342: 655-659 (den Daas). This 8-way rejection is respectfully traversed.

The Examiner cites eight (8) documents to support the obviousness rejection of Claims 21 and 22. *See* 2 *Chisum on Patents* § 5.04(1)(e)(vi) ("[t]he requisite prior art suggestion to combine [references] becomes less plausible when the necessary elements can only be found in a large number of references..."); *see also Ling-Temco-Vought, Inc..*, 372 F.2d at 268–69 ("[i]t is apparent that the more numerous the references and the more remote the cited art from the subject matter of the patent in suit, the less likely it becomes that a person having ordinary skill in the art would have arrived at the result reached by the patent in suit"); *Eli Lilly & Co.*, 2004 WL 1724632, at *23 (citing *Chisum*). Additionally, Claims 21 and 22 ultimately depend from Claim 10. Although not specifically rejected, a presumption of *prima facie* obviousness of Claim 10 (and thus of any claim dependent therefrom) over Nichols, Corrigan, Pfeiffer, Bronzava, Marquis, Rimpler, Dinan, and den Daas, or any combination of the 8 documents, does not exist. Applicant incorporates its argument set forth in the 10 February 2010 response, as (1) the results of the 7 esters tested in den Daas indicated that at least 4 of the esters did not have activity, and den Daas does not

disclose, teach or suggest carbamate, carbonate, ketal, acetate, phosphate, phosphonate, sulfate or sulfonate prodrugs and (2) den Daas fails to cure the deficiencies of Nichols, Corrigan, Pfeiffer, Bronzava, Marquis, Rimpler, Dinan, or any combination thereof, because the fact remains that rotigotine was not known to have antidepressant activity prior to the present invention. Therefore, the eight (8) cited documents, alone or in combination, fail to establish a presumption of *prima facie* obviousness of Claim 10.

Notwithstanding the Examiner's comments with regard to Claims 21 and 22, each of Claims 21 and 22 depend from Claim 10 and are therefore nonobvious for at least the same reasons Claim 10 is nonobvious over the 8-way combination of Nichols, Corrigan, Pfeiffer, Bronzava, Marquis, Rimpler, Dinan, and den Daas.

Withdrawal of the present 35 U.S.C. §103(a) rejection is respectfully requested.

4. Conclusion

It is believed that all of the stated grounds of rejection are properly traversed, accommodated, or rendered moot herein. Applicant therefore respectfully requests that the Examiner reconsider and withdraw all presently outstanding rejections. It is believed that a full and complete response has been made to the present Action and that the application is in condition for allowance.

If personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number below.

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